

PM3006372994

The Main biomarkers that will be discussed in the Draft CSR revision are the 24 biomarkers listed in the statistical section of the report. Please see the attached document for the list of these biomarkers.

The following changes will be made to the Draft CSR with no extra cost.

Results for each biomarker will be added to the narrative of the report. There will be *statistical results* and *biological (analytical) results*. Harrogate/Madison labs should provide the biological results.

The analytical labs should provide a paragraph for each of the biomarker listed in the attachment. This paragraph should describe the analytical results in terms of assay validation, variability, and any other important scientific finding that are of interest to client. Covance CRU will present any results necessary that the analytical group may request to fulfill this task. In addition, we suggest that analytical groups (INBIFO and Harrogate) provide a report discussing the differences/nuances in methods used by the two laboratories. This information will be incorporated into the CSR.

1. A new Table of Contents will be generated to re-structure the narrative section of the report.
2. The report will clearly state that the sponsor rejected the validation of the NNAL and the NNAL-glucuronide and any interpretation of this data should be made with caution.
3. Description of biomarkers that showed less than optimal results will be added (e.g. ACN, MDA, NNAL).
4. A list of biomarkers that need to be refined will be added (input required from analytical labs).
5. In-text reference to the number of cigarettes used in the calculation will be added.
6. Within the text of the report narrative (Text portion only) and in-text tables, the units for the results will be updated where necessary to give more manageable numbers.
7. "Similar but weaker relationships were seen between the average number of cigarettes smoked per day and 8-epi-PGF2alpha. Similar trends were observed with most biomarkers of exposure and biomarkers of effect." This paragraph will be reworded.
8. A discussion will be added in the report stating that outliers were verified with analytical labs and no reasons were found to exclude them from the analysis.
9. More discussion of statistical analysis results of safety data will be added in the report. Please provide us with a definition of "significant difference". This definition will be used to expand on the discussion of the safety data.
10. INBIFO report needs to be modified. Please see your comment in point 21 and the corresponding response that we have provided.
11. The reasons behind the use of compound symmetry will be provided.
12. In-text tables that you have proposed will be added to expand on the display and the interpretation of the exposure response modeling.

13. Recalculation of the intra- and inter-subject variability will be done and an in-text table will be added (see Table 14.1.1-8). In addition, more description and interpretation of the covariance parameters used to determine the intra- and inter-subject variability will be added.
14. More statements and descriptions will be added to describe the procedure of linear transformation of the nonlinear model and the way multiple regression was used to obtain initial estimates.
15. Definitive conclusions regarding adequate biomarkers will be added.
16. Issues regarding the questionnaire will be added.
17. No additional analyses are planned.

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